

BRIEF REPORT

Novel *EWSR1::TEAD3* Fusion in an Adolescent With a Highly Aggressive Peritoneal Mesothelioma

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ABSTRACT

Malignant peritoneal mesothelioma (MPM) is an exceptionally rare entity in children and adolescents, exhibiting distinct clinicopathological features compared to its adult counterpart. Unlike adult cases, it typically occurs without a history of asbestos exposure or *BAP1* inactivation. Although several driver gene fusions have been documented, the primary oncogenic triggers and molecular pathways involved remain largely undefined. Herein, we present an 18-year-old male who presented with ascites and abdominal distension. Computed tomography imaging revealed diffuse thickening of the peritoneum, including the omentum and mesentery. Histopathological examination showed a neoplasm composed of a mixture of atypical epithelioid and spindled cells infiltrating the adipose tissue. Immunohistochemically, the tumor cells were positive for cytokeratin, calretinin, CK5/6, and D2-40, and negative for CK20, MOC-31, and Ber-EP4, supporting the diagnosis of a biphasic mesothelioma. Molecular genetic studies identified a novel *EWSR1::TEAD3* gene fusion. This is the first reported case of a peritoneal mesothelioma harboring this fusion.

1 | Introduction

Mesothelioma is an uncommon and aggressive neoplasm originating from mesothelial cells, of either pleura or peritoneum, most commonly diagnosed in middle-aged and elderly individuals. While well-documented in adults, it is exceptionally rare in the pediatric population [1]. Epidemiological data suggest that less than 2%–8% of all mesothelioma cases manifest within the first two decades of life [2].

Notably, distinct clinicopathologic features differentiate pediatric malignant mesotheliomas from their adult counterparts [3]. In contrast to the striking male predominance observed among adults, pediatric cases exhibit an almost equal gender distribution. Anatomically, pleural origin predominates in adults;

however, in pediatric patients, peritoneal involvement is nearly as frequent as pleural involvement. Furthermore, the clinical course in children has often been associated with a more favorable outcome compared to adults, though aggressive cases, as presented here, do occur. The pathogenesis of mesothelioma in children remains largely elusive and appears distinct from that in adults. A well-established difference is the lack of a clear association with asbestos exposure in the vast majority of pediatric cases. Moreover, unlike adult mesotheliomas, which frequently harbor *BAP1* gene alterations, pediatric cases typically lack *BAP1* inactivation. Emerging molecular investigations have identified recurrent gene fusions in a subset of mesotheliomas affecting young patients, indicating a distinct oncogenic mechanism. These include fusions such as *EWSR1/FUS-ATF1* [4], as well as *MAP3K8* [5], and *ALK* rearrangements [3].

Qixing Gong and Jia Wei contributed equally to this work.

We herein report a clinically aggressive case of peritoneal mesothelioma in an 18-year-old male, who succumbed to the disease merely 2 months after diagnosis. Previously identified fusion partners for *EWSR1/FUS* in mesothelioma include *ATF1* and *YY1* [6]. In this case, we identified a novel *EWSR1::TEAD3* fusion, establishing *TEAD3* as the third reported fusion partner in *EWSR1/FUS*-rearranged mesothelioma.

2 | Case Presentation

2.1 | Clinical Findings

An 18-year-old male patient with no history of direct or indirect asbestos exposure, pleural disease, or other malignancies was admitted with complaints of abdominal pain and worsening distension for 4 days, accompanied by a single episode of vomiting. Ultrasound examination of the whole abdomen identified anechoic fluid collections around the liver and spleen and in the lower abdominal cavity, indicating ascites. Positron emission tomography-computed tomography (PET-CT) imaging demonstrated thickening of the omentum, peritoneum, and mesentery (Figure 1A), accompanied by multiple flocculent exudative shadows and increased fluorodeoxyglucose (FDG) uptake. Pelvic and abdominal fluid collections were also observed, alongside mildly enlarged lymph nodes within the abdominopelvic region. These radiologic features suggested either an infectious or metastatic malignancy etiology, with tuberculous peritonitis being the most probable diagnosis. A tuberculous peritonitis was excluded by negative results for the T-SPOT.TB assay, tuberculosis antibody test, and tuberculin skin test. A laparoscopic peritoneal biopsy was conducted. During the procedure, significant ascites were observed within the abdominal cavity, along with extensive nodules on the peritoneum. Additionally, the entire omentum exhibited rigidity, enveloping the small intestine.

2.2 | Histopathology and Immunohistochemical Study

Microscopically, tumor cells diffusely infiltrated into adipose tissue (Figure 1B). At higher magnification, the tumor cells displayed epithelioid, spindle, or irregular morphology, with abundant eosinophilic to clear cytoplasm. Certain regions bore resemblance to deciduioid mesothelioma, featuring cohesive sheets of large polygonal cells with abundant eosinophilic cytoplasm and vesicular nuclei (Figure 1C). Moreover, in some areas, these epithelioid cells were closely intermixed with a population of atypical spindle cells possessing elongated hyperchromatic nuclei and prominent nucleoli (Figure 1D). Both cellular components were embedded within a hyalinized stroma. Evidence of tumor necrosis and inflammatory cell infiltration was observed, with mitotic figures averaging two to three per 10 high-power fields.

By immunohistochemistry, the tumor cells exhibited diffuse and strong cytoplasmic expression of CK-pan (Figure 1E) and were focally positive for Calretinin (Figure 1F), CK5/6, CK7, and D2-40 (Figure 1G). The stains for WT-1, CK20, MOC-31, Ber-EP4, Villin, CDX-2, LCA, S-100, CD34, SATB2, CD31, ERG, FLI-1, MUC-4, Synaptophysin, and ALK (D5F3) were negative. Notably, BAP1 and INI-1 (SMARCB1) showed retained nuclear expression. The Ki-67 index was approximately 10%. The final diagnosis was peritoneal biphasic mesothelioma.

3 | Molecular Analysis

DNA extracted from the tumor tissue underwent targeted DNA NGS, which detected an *EWSR1* breakpoint within intron 8 (Figure 2A). However, multiple genomic fragments, including *TEAD3*, were fused to *EWSR1* at the DNA level. To

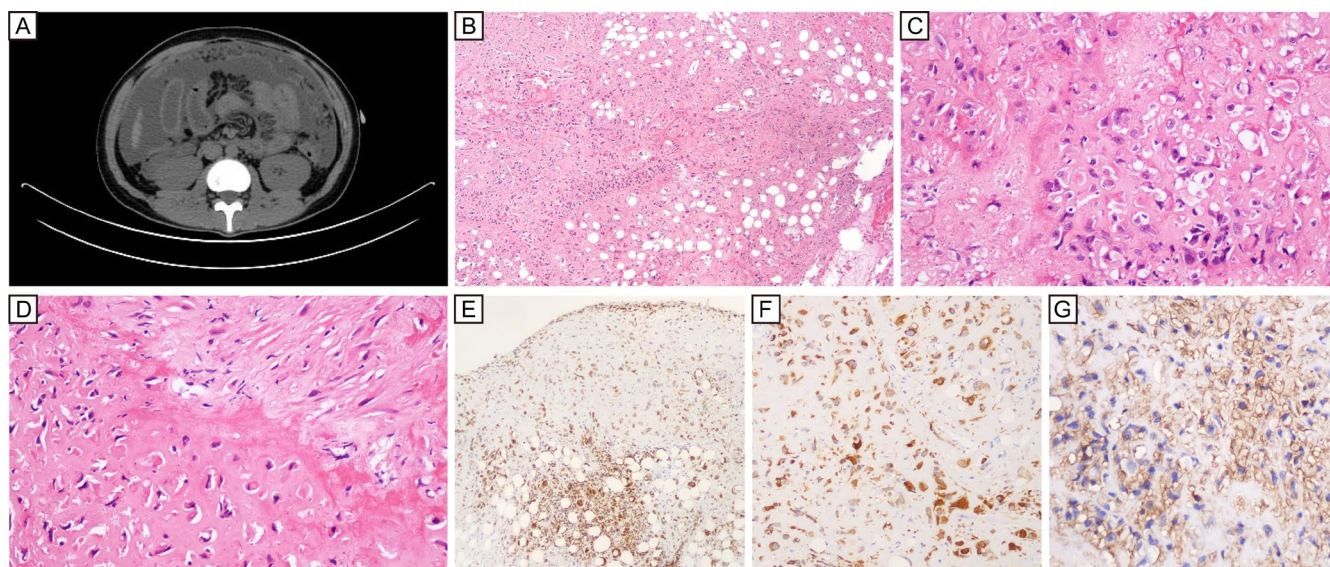


FIGURE 1 | Imaging studies and microscopic features of the peritoneal mesothelioma. (A) Computed tomography (CT) scan demonstrated thickening of the omentum, peritoneum, and mesentery, accompanied by multiple flocculent exudative shadows, along with pelvic and abdominal fluid accumulation. (B) Tumor cells diffusely infiltrated the adipose tissue, forming a honeycomb-like pattern. (C) Majority of tumor cells had an epithelioid morphology, characterized by abundant eosinophilic to clear cytoplasm and moderate cellular atypia. (D) Some regions contained spindle-shaped cells intermixed with epithelioid cells, indicating a biphasic cellular composition. (E–G) Immunohistochemically, the tumor cells expressed diffuse and strong positivity for CK-pan (E), focal cytoplasmic positivity for Calretinin (F), and focal membranous positivity for D2-40 (G).

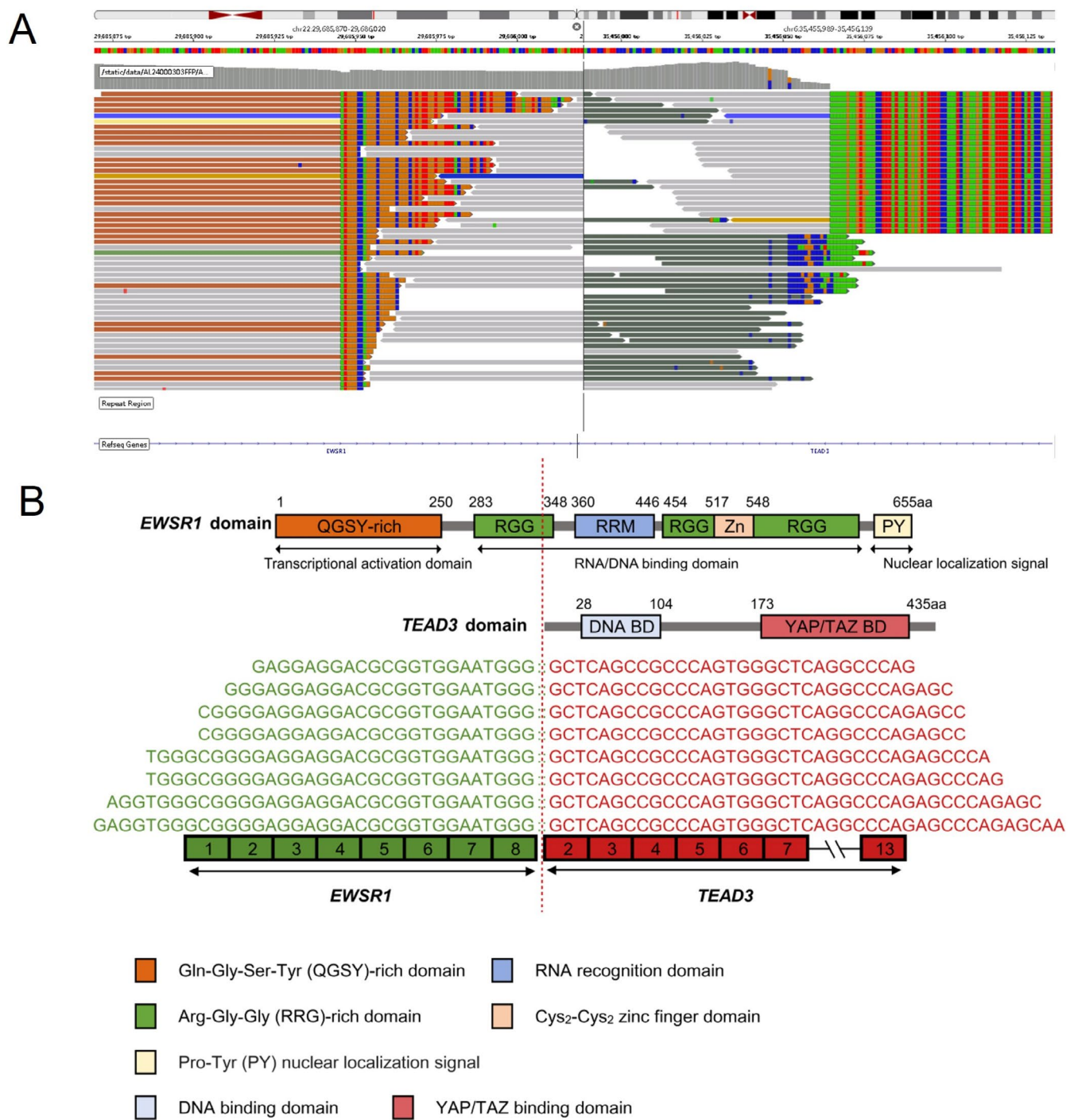


FIGURE 2 | Molecular characterization of the *EWSR1::TEAD3* rearrangement. (A) DNA-based NGS identified a breakpoint in intron 8 of *EWSR1*, but multiple genomic fragments, including *TEAD3*, were found fused to *EWSR1*, preventing definitive fusion partner assignment at the DNA level. (B) Targeted RNA sequencing confirmed an *EWSR1::TEAD3* fusion transcript, and the corresponding breakpoint, exon structure, and predicted chimeric protein are shown.

characterize the fusion transcript, total RNA isolated from the tumor tissue was analyzed using a targeted RNA NGS panel, which identified an *EWSR1::TEAD3* fusion. This fusion joined exon 8 of *EWSR1* to exon 2 of *TEAD3*, including a 5' UTR segment encoding 17 amino acids upstream of exon 2. This UTR segment served as a linker, preserving the open reading frame and maintaining the integrity of the resulting fusion protein. Structurally, the predicted *EWSR1::TEAD3* fusion protein retained the N-terminal transcriptional activation domain of

EWSR1 and the complete *TEAD3* protein, including its DNA-binding domain (DBD).

4 | Treatment and Follow-Up

Upon diagnosis, the extensive tumor burden precluded cytoreductive surgery. The patient underwent one course of hyperthermic intraperitoneal chemotherapy (HIPEC) with poor tolerance

and subsequently developed intestinal obstruction, leading to multiple organ failure. He succumbed to the mesothelioma only 2 months after the initial diagnosis.

5 | Discussion

Peritoneal malignant mesothelioma (MPM) represents an exceedingly uncommon neoplasm among pediatric and adolescent populations, with its clinical and pathological features in this group remaining inadequately characterized due to its rarity. In contrast to adult cases, which have established risk factors, including asbestos exposure, irradiation, chronic inflammation, the etiological determinants in pediatric and adolescent populations remain predominantly unknown. In adult patients, the molecular landscape of peritoneal mesothelioma largely mirrors that of its pleural counterpart, being predominantly characterized by inactivating mutations in tumor suppressor genes, particularly *BAP1*, *NF2*, *CDKN2A*, *CDKN2B*, and *PBRM1* [7, 8]. However, in pediatric cases, the genomic profile is distinct and often lacks classic *BAP1* alterations [9]. Comprehensive molecular testing continues to identify rare genomic subgroups, including mesotheliomas harboring oncogenic rearrangements in genes such as *ALK* and *EWSR1* [3–4, 6], typically associated with epithelial or biphasic histology. Our case of pediatric peritoneal mesothelioma harbors a novel *EWSR1::TEAD3* fusion, shows no history of asbestos exposure, and exhibits a mixture of atypical epithelioid and spindle cells, largely reflecting the clinical and genomic features of this rare molecular subtype.

The *EWSR1* gene encodes a well-characterized RNA-binding protein that is notoriously promiscuous, frequently serving as a 5' fusion partner with diverse 3' partner genes across a broad spectrum of tumors. Its principal oncogenic contribution lies in its potent N-terminal transactivation domain [10]. To date, two *EWSR1/FUS* fusion partners have been reported in mesothelioma, *ATF1* and *YY1*. With the addition of the third partner, *TEAD3*, described here, these genes share a unifying feature: they all encode DNA-binding transcription factors. When fused to *EWSR1* or *FUS*, the resulting chimeric proteins act as aberrant transcriptional activators. Although all are transcription factors, each responds to distinct upstream signaling pathways. *ATF1*, along with *CREB1* and *CREM*, belongs to the *CREB/ATF* family of bZIP transcription factors, which mediate transcriptional responses to stress and growth signals through the cAMP/PKA pathway. In contrast, *YY1* is a zinc finger transcription factor involved in epigenetic and chromatin regulation. *TEAD3* belongs to the *TEAD* family of transcription factors, which serve as key downstream effectors of the Hippo signaling pathway, a tumor suppressive cascade that limits cell proliferation and promotes apoptosis [11]. The *TEAD3* protein contains two critical domains: an N-terminal TEA DBD and a C-terminal YAP/TAZ-binding domain. Under physiological conditions, *TEAD3* activity is tightly regulated by interaction with YAP or TAZ, which are themselves controlled by the Hippo kinase cascade [12]. In the proposed *EWSR1::TEAD3* fusion, the chimeric protein is predicted to consist of the N-terminal transactivation domain of *EWSR1* fused to the entire *TEAD3* protein, including both its DNA-binding and YAP/TAZ-binding domains. This configuration likely results in Hippo pathway-independent transcriptional activation of *TEAD3* target genes involved in cell

proliferation, migration, and epithelial–mesenchymal transition (EMT) [13, 14].

Our case required differentiation from the recently described *EWSR1::CREM*-rearranged intra-abdominal malignant epithelioid neoplasm [15, 16]. Histologically, the tumor showed biphasic epithelioid and spindle cell components, with immunohistochemical findings supporting mesothelial differentiation. Markers typical of *EWSR1::CREM* neoplasms, such as WT-1, MUC4, ALK, and Synaptophysin [16], among others, were absent. These features favor a diagnosis of peritoneal biphasic mesothelioma.

The management of peritoneal mesothelioma involves a multidisciplinary approach, including surgery, chemotherapy, immunotherapy, cytoreductive surgery, and HIPEC. Despite these intensive treatment modalities, the disease frequently exhibits a rapid and fatal progression, with an estimated median survival of only 6–12 months [17]. Nevertheless, some studies indicate a comparatively more favorable prognosis in younger patients relative to adults [1, 18]. This apparent survival benefit is primarily attributed to two factors. First, the higher incidence of peritoneal mesothelioma in this population, which is associated with a greater likelihood of achieving complete surgical resection, a critical determinant of improved survival outcomes [2]. Second, certain cohorts have included cases of indolent multicystic peritoneal mesothelioma (MCM) in survival analyses, potentially biasing the data toward better prognoses [1]. In the present case, however, the prognosis was poor. This outcome was driven by several factors: advanced disease and poor performance status at diagnosis; limited response to HIPEC; aggressive biphasic histology; and likely, the *EWSR1::TEAD3* fusion contributing biologically to the tumor's invasiveness and treatment resistance.

In summary, we report a case of peritoneal mesothelioma in an 18-year-old male with a poor prognosis. Although rare, this case underscores the importance of including peritoneal mesothelioma in the differential diagnosis of abdominal tumors in pediatric and adolescent patients. Additionally, we identified a novel *EWSR1::TEAD3* fusion in this patient, offering a valuable opportunity to elucidate the molecular mechanisms driving this aggressive malignancy.

Author Contributions

Sheng Xiao and Qixing Gong: conceptualization, drafting, revising, final approval of the version. Qixing Gong and Jia Wei: acquisition of data, drafting.

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The authors have nothing to report.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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